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Original article

The efficacy of fibrin sealant in knee surgery: A meta-analysis



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ABSTRACT

Background: Fibrin sealant is frequently used in knee surgery as an adjuvant method for reducing post-operative bleeding, however, there is no consensus regarding the efficacy of fibrin sealant.

Hypothesis: Fibrin sealant achieves better efficacy in terms of blood loss control, transfusion rate and units in knee surgery compared with controls.

Methods: A search of the Cochrane Collaboration (2013 Issue 09), Embase (1974–2013.09), PubMed (1966–2013.09) and Chinese databases (up to 2013.09) were conducted. The Cochrane Collaboration's tool was used to assess for bias and data were analyzed by RevMan 5.29 software.

Results: This study included nine RCTs and four prospective comparative trials with a total of 1299 patients. Compared to the control, fibrin sealant achieved a decrease in hemoglobin reduction [MD = 1.14, 95% CI (0.61–1.67)], transfusion rate [OR = 0.36, 95% CI (0.25–0.51)], transfusion units [MD = 0.47, 95% CI (0.24–0.71)], hospital stay [MD = 2.22, 95% CI (0.56–3.88)] and the incidence of complications [OR = 0.56, 95% CI (0.38–0.83)]. And it also reduced total blood loss, while there was no significant difference [MD = 155.83, 95% CI (–525.02–213.15)].

Conclusion: Patients undergoing knee surgery would benefit from high-dose fibrin sealant with reduced transfusion rate and unit, hospital stay and complications, while they might benefit little from it in total blood loss. However, the effects of a low-dose of fibrin in knee surgery remain inconclusive.

Level of evidence: Level III.

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1. Introduction

Serious knee arthritis can lead to varying degrees of pain and/or functional disability, including decreased flexion and extension ability [1]. Total knee arthroplasty (TKA) and total knee replacement (TKR) are both common, successful surgeries that are widely used to treat patients with serious knee arthritis [2]. TKA and TKR are frequently followed by postoperative bleeding and often result in significant blood loss. The drain output from patients, measured using knee drains, ranges from 1200 mL to 1800 mL [2,3], though this can be even higher due to hidden blood loss [4,5]. A tourniquet is always used intra-operation, but a meta-analysis by Tai et al. showed that this could only save operation time [6], not reduce blood loss [7]. In addition, patients managed with a tourniquet can have higher risks of thromboembolic complications postoperation [8].

Fibrin sealant is comprised mostly of fibrinogen and human thrombin [9] and can initiate the last phase of physiological blood coagulation [10]. Although it has been used for decreasing postoperative blood loss in surgery for 20 years, the effects of fibrin sealant on knee surgery remain unclear. Some studies have indicated that additional fibrin sealant significantly reduces blood loss, thus, reducing the need for blood transfusion [2,11,12]. Other studies have shown that the difference in blood transfusion requirement between fibrin sealant groups and control groups were not statistically significant [13,14]. Furthermore, the cost of the additional fibrin sealant is three times greater than that of the required blood transfusion [2].

To date, there is no consensus in the medical community with regard to the efficacy of fibrin sealant in knee surgery and there is limited evidence from systematic reviews or meta-analyses. In this study, we evaluate the efficacy and safety of fibrin sealant in knee surgery through analysis of relevant randomized controlled trials (RCTs) and prospective comparative studies. The hypothesis of the present study was that fibrin sealant achieves better efficacy in knee surgery compared with controls. The use of fibrin sealant allows decreasing the total

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blood loss, the transfusion rate and the mean transfusion unit in TKR.

2. Materials and methods

2.1. Literature search

Online databases, such as the Cochrane Library (2013 Issue 09), Embase (1974–2013.09), PubMed (1966–2013.09) and the Science Citation Index Expanded were searched up to September 2013. In addition, our search included the following Chinese databases: the Chinese biomedicine literature database (CMB), the Chinese periodical full text database (CNKI) and the Wan fang database, and they were all searched up to September 2013. A range of search terms were used: “(knee surgery OR total knee arthroplasty OR TKA OR total knee replacement OR TKR) AND (fibrin sealant OR fibrin glue OR fibrin tissue adhesive)”. Based on the primary search results, future supplementary searches included reading abstracts, studies, conference proceedings and citations.

2.2. Inclusion criteria

Only published RCTs and prospective comparative studies were included, regardless of blinding and allocation concealment. Reviews, case reports and experience-based communications were excluded from the study. Patients suffering from serious bilateral or unilateral knee joint disease who were willing to receive total knee arthroplasty or total knee replacement were eligible for inclusion in the study. Participants were divided into two groups: the treatment group was treated with fibrin sealant during surgery and the control group was not. Other interventions, including drugs and functional recovery training, were permitted only when comparable between the two groups.

The main outcome measures were total blood loss, transfusion rate, and transfusion units. Secondary outcome measures were Hb reduction, drain-out volume, hospital stay, and complications.

2.3. Data extraction and quality assessment

All studies obtained from the initial searches were independently assessed for eligibility by two researchers according to specific characteristics. Only studies evaluating the effectiveness of fibrin sealant in TKA or TKR were considered and analyzed. Next, two researchers independently extracted the data for the outcome measures. Three reviewers independently performed a methodological quality assessment on the studies according to the Cochrane Handbook [15], based on methods of randomization, allocation concealment, blinding, comparable baseline, follow-up, and free of selective reporting. Any disagreements about eligibility, methodological quality and data were resolved through discussion.

2.4. Statistical analysis

Statistical analysis was performed using RevMan 5.29. Heterogeneity was estimated using the χ^2 test and was considered to be significant when $I^2 > 50\%$; in this case, a random-effects model was applied. When there was not significant heterogeneity, a fixed-effects model was applied. Effect size was expressed using a relative odds ratio (OR) for dichotomous data and mean differences (MD) for continuous data and all 95% confidence intervals (95% CI) were presented. Subgroup meta-analysis, including low-dose (≤ 5 mL) and high-dose (> 5 mL) [9] was conducted. Sensitivity analysis and publication bias were also performed.

3. Results

3.1. Flow diagram of trial selection

Nine RCTs [11–14,16,17,20–22] and four prospective comparative studies [2,13,18,23] assessing the use of fibrin sealant in patients who received knee surgery were retrieved from electronic databases. Of these, two studies reported data from one trial and both of them were included [13,23]. Another study contained three arms: two fibrin sealant arms (5 mL and 10 mL, respectively) and one control arm; we deemed this two independent trials [17]. The flow diagram (Fig. 1) illustrates the trial selection process from the results of the initial literature search to the final decision.

3.2. Characteristics and methodological quality of included studies

Table 1 shows specific characteristics including sample size, age, preoperative Hb level, and intervention. A total of 1299 patients were included in the study. The methodological quality of each study was assessed using the Cochrane handbook 5.0.1 and the results are shown in Table 2.

3.3. Effect size of interventions

3.3.1. Blood loss

Both drain-out blood loss and total blood loss were reported. A total of seven studies [11,14,16–18,20,22] reported data on drain-out blood loss and there was heterogeneity between them ($I^2 = 94\%$). The random-effects model revealed that fibrin sealant significantly reduced drain-out blood loss by a mean of 316.81 mL compared to the control group [95% CI (180.76–452.87); $P < 0.01$]. A subgroup analysis of four studies [2,16,19,20] reported total blood loss and random-effects model showed that fibrin sealant reduced the total blood loss by a mean of 155.93 mL, but it failed to reach statistical significance [95% CI (–525.02–213.15); $I^2 = 86\%$], as shown in Fig. 2.

To further explore the dose-effect, we also performed another subgroup analysis. A subgroup analysis of two studies [11,17] showed that a low-dose of fibrin sealant reduced drain-out put by a mean of 391.28 mL [95% CI (313.10–469.47); $P = 0.60$; $I^2 = 0\%$]. A subgroup analysis of four studies [14,17,18,22] revealed that a high-dose of fibrin sealant obtained a reduction in blood loss by a mean of 319.09 mL [95% CI (93.2–544.98); $P = 0.006$; $I^2 = 96\%$], as shown in Fig. 3.

3.3.2. Transfusion rate

Eight studies [2,11–14,17,19,20] were analyzed for transfusion rate. The fixed-effects model revealed that fibrin sealant reduced transfusion rate compared to control group [OR = 0.36; 95% CI (0.25–0.51); $I^2 = 0\%$]. A subgroup analysis of three studies [2,11,17] showed that a low-dose of fibrin sealant reduced transfusion rate [OR = 0.27; 95% CI (0.14–0.50); $I^2 = 0\%$]. Finally, a subgroup analysis of seven studies [2,12–14,17,19,20] showed that a high-dose of fibrin sealant reduced transfusion rate compared to the control group [OR = 0.40; 95% CI (0.27–0.62); $I^2 = 42\%$], as shown in Fig. 4.

3.3.3. Blood transfusion unit

Due to significant heterogeneity ($I^2 = 78\%$), the random-effects model was applied and this revealed that fibrin sealant reduced blood transfusion units by a mean of 0.47 U compared to the control group [95% CI (0.24–0.71); $P < 0.0001$]. A subgroup analysis of two studies [2,17] showed that a low-dose of fibrin sealant reduced blood transfusion units by a mean of 0.45 U [95% CI (0.17–0.73); $P = 0.73$; $I^2 = 0\%$]. A subgroup analysis of five studies [11,13,17–19] showed that high-doses of fibrin sealant reduced blood transfusion

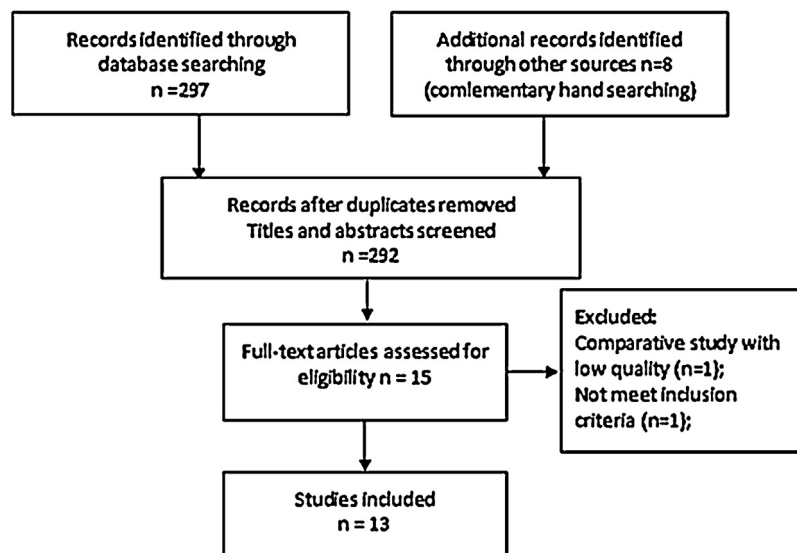


Fig. 1. Flow diagram shows literature process from initial search to final selection result.

Table 1
Characteristics of trials included in this meta-analysis.

Study	Year	Study design	Case (T/C, n)	Age (T/C, y)	Pre-operative Hb (T/C, g/dL)	Intervention
Massin et al. [2]	2012	pCS	31/31	69.2 ± 10.7/72 ± 8	14.0 ± 1.0/13.0 ± 1.2	5 mL FS vs blank control
Kluba et al. [21]	2012	pRCT	12/12	70.8 ± 5.6/71.0 ± 10.6	–	2 mL FS vs blank control
Sabatini et al. [11]	2012	pRCT	35/35	70.7 ± 6.4/70.4 ± 6.7	13.2 ± 1.3/13.5 ± 1.5	5 mL FS vs postoperative blood recovery and reinfusion
Notarnicola et al. [17]	2012	pRCT	30/30	69.2 ± 8.2	13.4 ± 1.2/13.7 ± 1.1	5 mL FS vs blank control
Levy et al. [16]	1999	pRCT	29/29	68.9 ± 6.3/70.2 ± 8.2	–	10 mL FS vs blank control
Skovgaard et al. [22]	2012	pRCT	24/24	33–81	–	5–10 mL FS vs blank control
Wang et al. [14]	2001	pRCT	25/28	–	13.5 ± 0.3/13.2 ± 0.3	10 mL FS vs saline
Wang et al. [12]	2003	pRCT	107/97	68.2 ± 8.3/68.9 ± 8.7	3.0 ± 0.2/3.5 ± 0.2	10 mL FS vs blank control
Everts et al. [13]	2006	pCS	85/80	69.4 ± 9.1/67.4 ± 9.9	13.6 ± 1.1/13.7 ± 1.1	10 mL FS vs blank control
Everts et al. [23]	2007	pCS	85/80	69.4 ± 9.1/67.4 ± 9.9	13.6 ± 1.1/13.7 ± 1.1	9 mL FS vs blank control
Spinarelli et al. [18]	2011	pCS	64/46	–	–	10 mL FS vs blank control
Molloy et al. [19]	2006	pRCT	50/50	–	11.9 ± 0.9/12.0 ± 0.7	10 mL FS vs blank control
Aguilera et al. [20]	2001	pRCT	43/43	72.6 ± 1.0/74.9 ± 7.0	13.4 ± 2.2/13.4 ± 1.2	6 mL FS vs blank control

T: treatment group; C: control group; FS: fibrin sealant; pRCT: prospective randomized controlled trials; pCS: prospective comparative study.

units by a mean of 0.48 U [95% CI (0.18–0.78); $P = 0.002$; $I^2 = 85\%$], as shown in Fig. 5.

3.3.4. Hemoglobin (Hb) reduction

Six studies reported Hb reduction [11,14,16–18] and the results revealed that fibrin sealant led to a significant decrease in Hb

reduction compared to the control group [MD = 1.14; 95% CI (0.61–1.67); $P < 0.01$; $I^2 = 86\%$]. A subgroup analysis of two studies [11,17] showed that low-dose fibrin sealant led to an Hb reduction by a mean of 0.68 mg/dL [95% CI (0.01–1.67); $P = 0.05$; $I^2 = 46\%$]. A subgroup analysis of four studies revealed that high-dose fibrin sealant also led to an Hb reduction by a mean of 1.34 mg/dL [95%

Table 2
Quality assessment of the included trials.

Study	Randomization	Allocation concealment	Blinding	Comparable baseline	> 80% follow-up	Free of selective reporting	Level
Massin et al. [2]	N	–	–	Y	Y	Y	C
Kluba et al. [21]	M	Unclear	Unclear	Y	Y	Y	C
Sabatini et al. [11]	M	Unclear	Unclear	Y	Y	Y	C
Notarnicola et al. [17]	Y, stratified random	Unclear	Y, double blind	Y	Y	Y	A
Levy et al. [16]	Y, centralized random	Y	Y, single blind	Y	Y	Y	A
Skovgaard et al. [22]	Y, random sequence	Y	Y, double blind	Y	Y	Y	A
Wang et al. [14]	M	Unclear	Y, single blind	Y	Y	Y	B
Wang et al. [12]	M	Unclear	Y, single blind	Y	Y	Y	B
Everts et al. [13]	N	–	–	Y	Y	Unclear	C
Everts et al. [23]	N	–	–	Y	Y	Unclear	C
Spinarelli et al. [18]	N	–	–	Y	Y	Unclear	C
Molloy et al. [19]	Y, block balance random	Y	Y, double blind	Y	Y	Y	A
Aguilera et al. [20]	Y, block balance random	Y	N	Y	Y	Y	A

N: the method was not used in the study; M: the method was mentioned, but there was not detailed description; Y: the method was reported with detailed description. Unclear: no relevant information was found in the study.

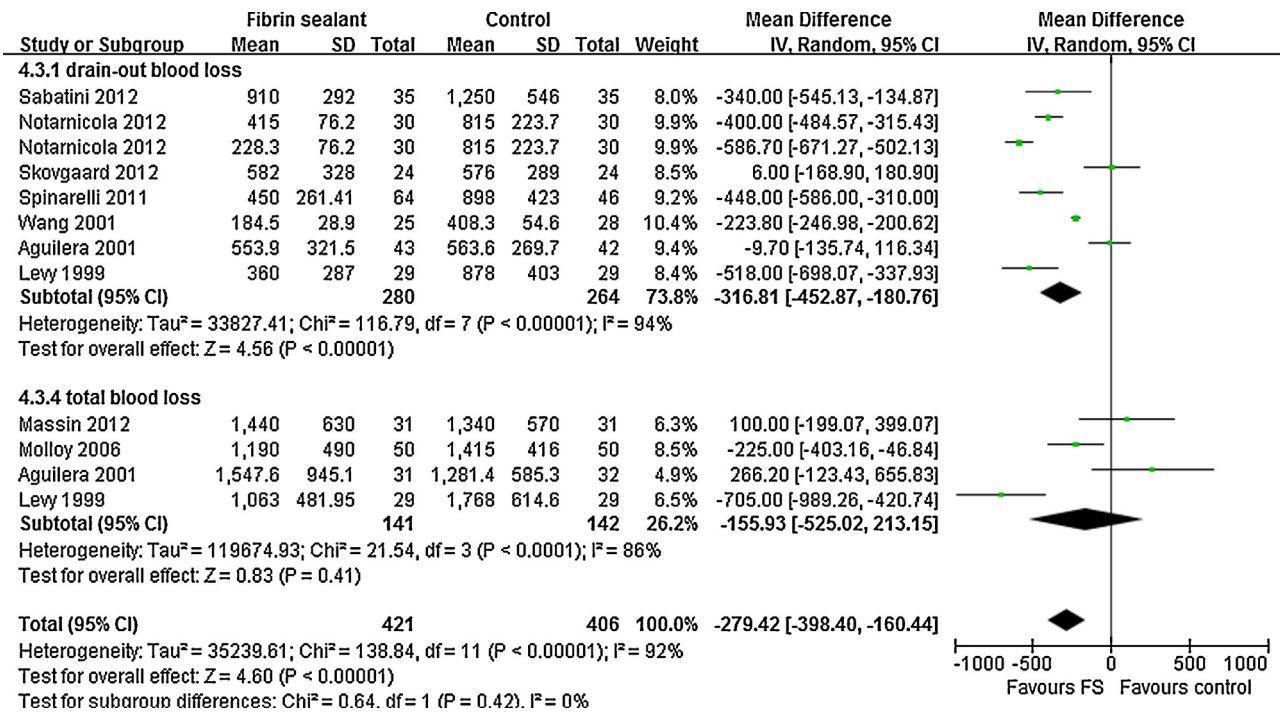


Fig. 2. Subgroup meta-analysis of blood loss between the two groups.

CI (0.58–2.10); $P = 0.0006$], as shown in Fig. 6 [14,16–18]. Due to heterogeneity ($I^2 = 91\%$), the random-effects model was used.

3.3.5. Hospital stay

Using the random-effects model ($I^2 = 93\%$), we discovered that fibrin sealant reduced hospital stay by a mean of 2.22 days compared to the control group [95% CI (0.56–3.88); $P = 0.009$]. A subgroup analysis of two studies [17,21] showed that a low-dose of fibrin sealant reduced hospital stay by a mean of 2.77 days compared to the control group [95% CI (0.39–5.14); $P = 0.02$; $I^2 = 54\%$]. A subgroup analysis of three studies [13,17,20] showed that a high-dose of fibrin sealant reduced hospital stay by a mean of 1.97 days compared to the control group [95% CI (-0.41–4.36); $P = 0.11$; $I^2 = 93\%$; Fig. 7].

3.3.6. The incidence of complications

A pooled analysis using the fixed-effects model ($I^2 = 28\%$) revealed a significant reduction in the incidence of complications in the treatment group [OR = 0.56; 95% CI (0.38–0.83); $P = 0.003$].

Three studies [11,12,16] reported fever and there was no significant difference between the groups [OR = 1.06; 95% CI (0.60–1.90); $P = 0.87$]. Three studies [11,14,23] reported hematomas and there was a significant difference [OR = 0.26; 95% CI (0.07–1.01); $P = 0.05$]. Three studies [16,17,19] reported thrombosis, and there was no significant difference [OR = 2.26; 95% CI (0.50–10.35); $P = 0.29$]. Two studies [12,23] reported arthropathy and there was a significant difference [OR = 0.15; 95% CI (0.04–0.58); $P = 0.65$]. Four studies [12,13,16,19] reported wound infection,

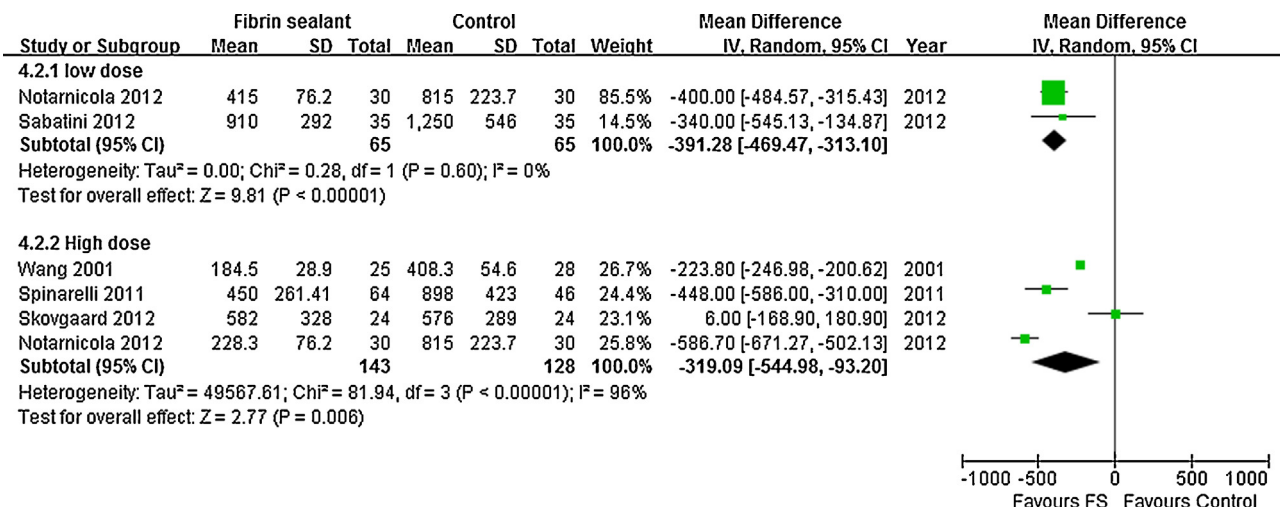


Fig. 3. Subgroup meta-analysis of drain output between the two groups.

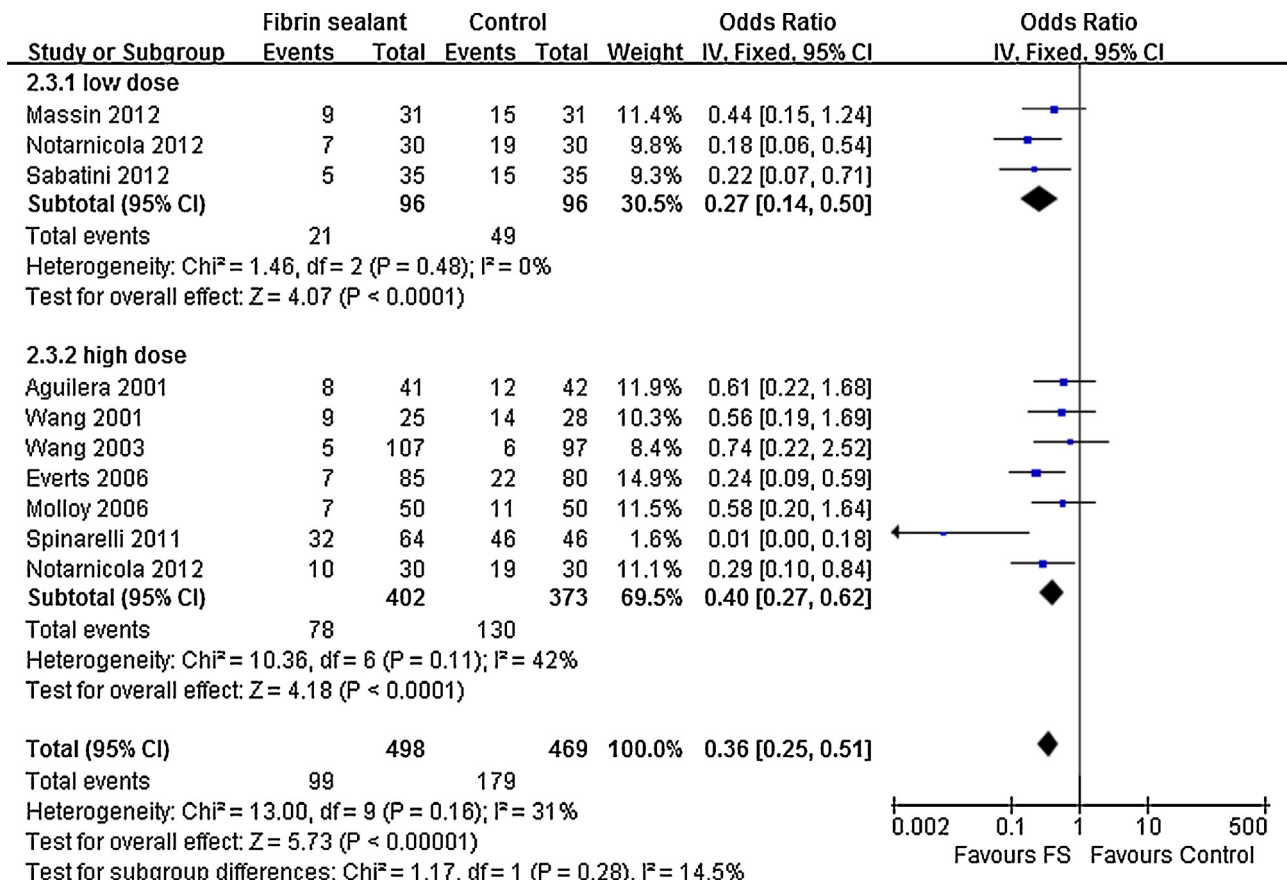


Fig. 4. Subgroup meta-analysis of the incidence of blood transfusion between the two groups.

and there was no significant difference [OR=0.47; 95% CI (0.16–1.39); $P=0.17$]. Only one study [13] reported that fibrin sealant could significantly reduce the incidence of wound leakage (Fig. 8).

3.3.7. Sensitivity analysis

Sensitivity analysis was performed by omitting the non-RCT [2,13,18,23] and the poor quality studies [11,21]. The results showed similar trend for a decrease in Hb reduction, total blood

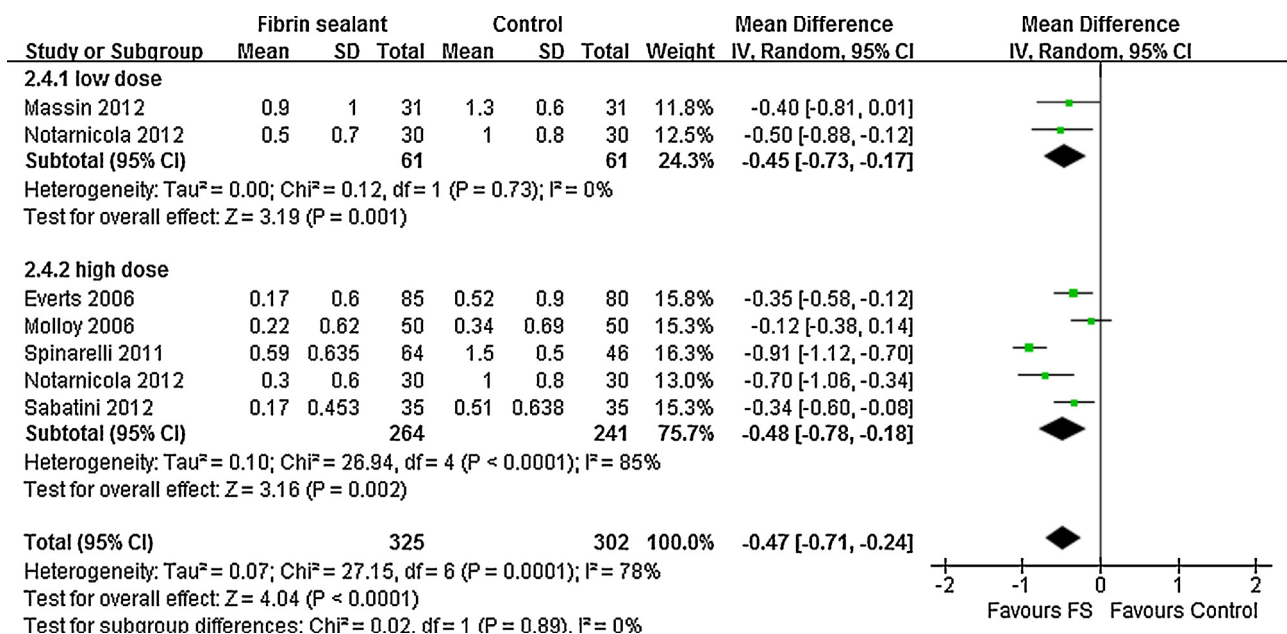


Fig. 5. Subgroup meta-analysis of blood transfusion unit between the two groups.

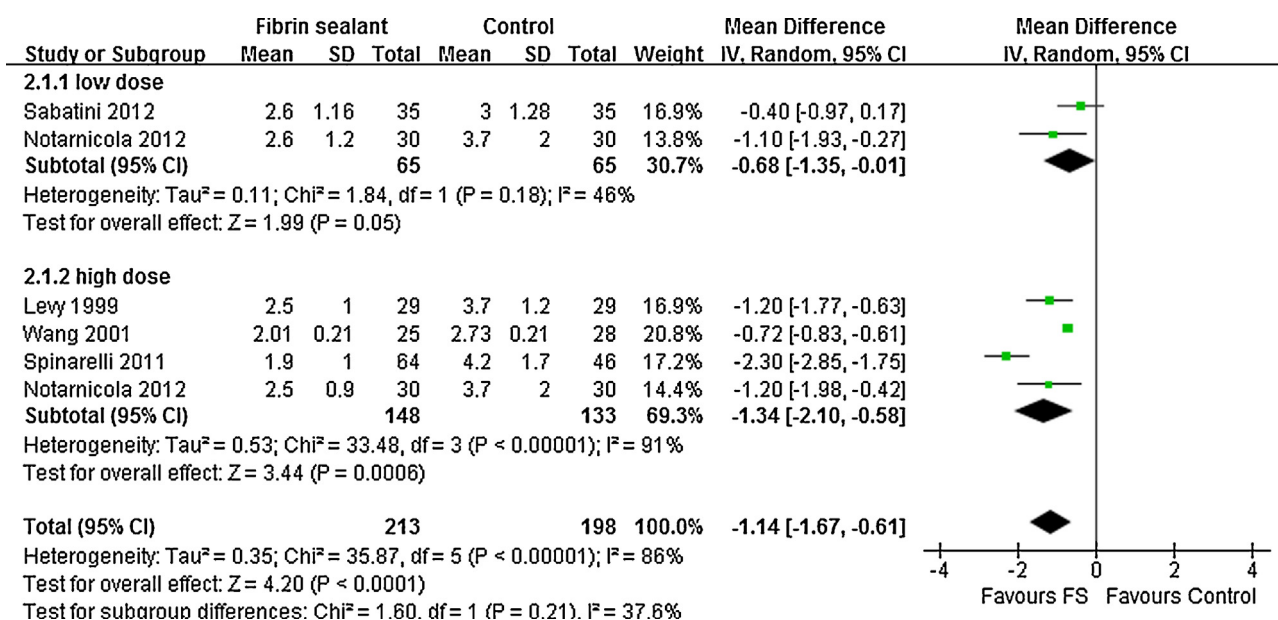


Fig. 6. Subgroup meta-analysis of hemoglobin reduction between the two groups.

loss, the transfusion rate, transfusion units, and hospital stay, while they showed different trend for a reduction in the incidence of complications.

3.3.8. Publication bias

Funnel plots were adopted to evaluate the publication bias. The shapes of funnel plots for Hb reduction, transfusion rate (Fig. 9), and the incidence of complications did not reveal asymmetry, indicating no evidence of publication bias.

4. Discussion

The present meta-analysis showed that the use of fibrin sealant might reduce the transfusion rate and transfusion units following TKR, but that the effect of reducing the total blood loss was not significant.

4.1. Blood transfusion

The group treated with fibrin sealant had a lower transfusion rate and transfusion units. After adjusting specific patient characteristics (such as age, sex, cardiovascular history, ASA score and anaemia severity), most studies followed protocol recommended by 1988 National Institutes of Health consensus conference indicating 8 g/dL as the lowest acceptable Hb concentration. It was noted that different protocols for blood transfusion were followed in two studies [7,10], and the transfusion criteria was Hb value less than 8.8 g/dL or 10 g/dL. So, they are more easily to order transfusion than others, and this would be a potential source of heterogeneity. Meanwhile, one study mentioned that the control group had a lower preoperative Hb level than treatment group [2], and therefore perhaps inducing a higher transfusion rate, which might influence the result.

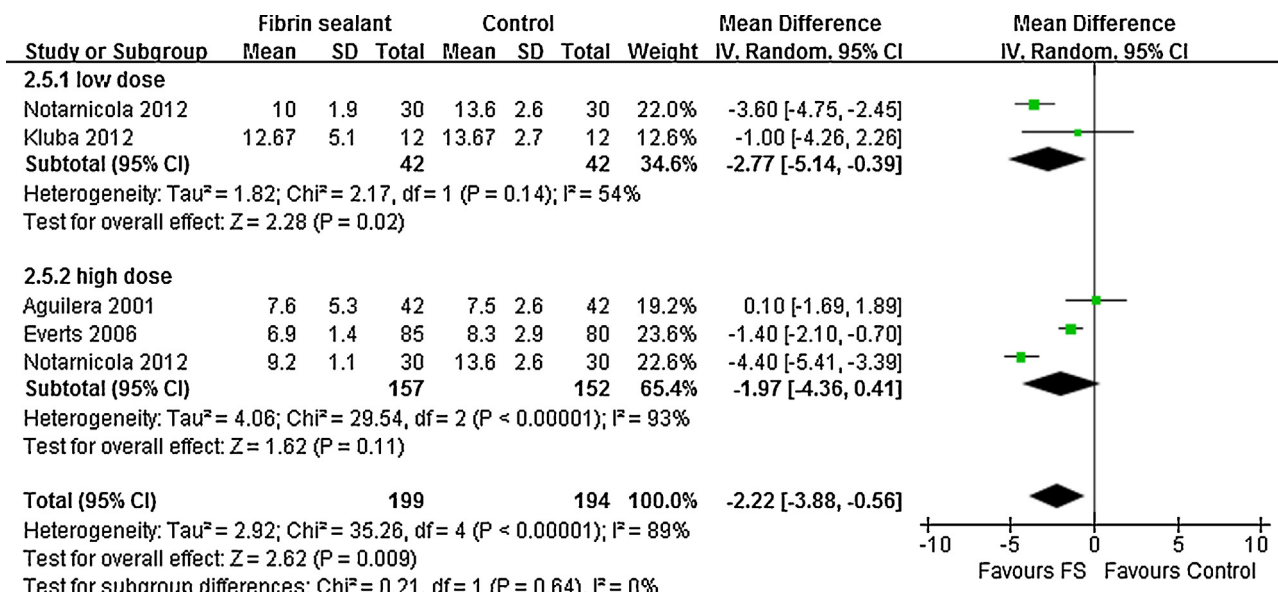


Fig. 7. Subgroup meta-analysis of hospital stay between the two groups.

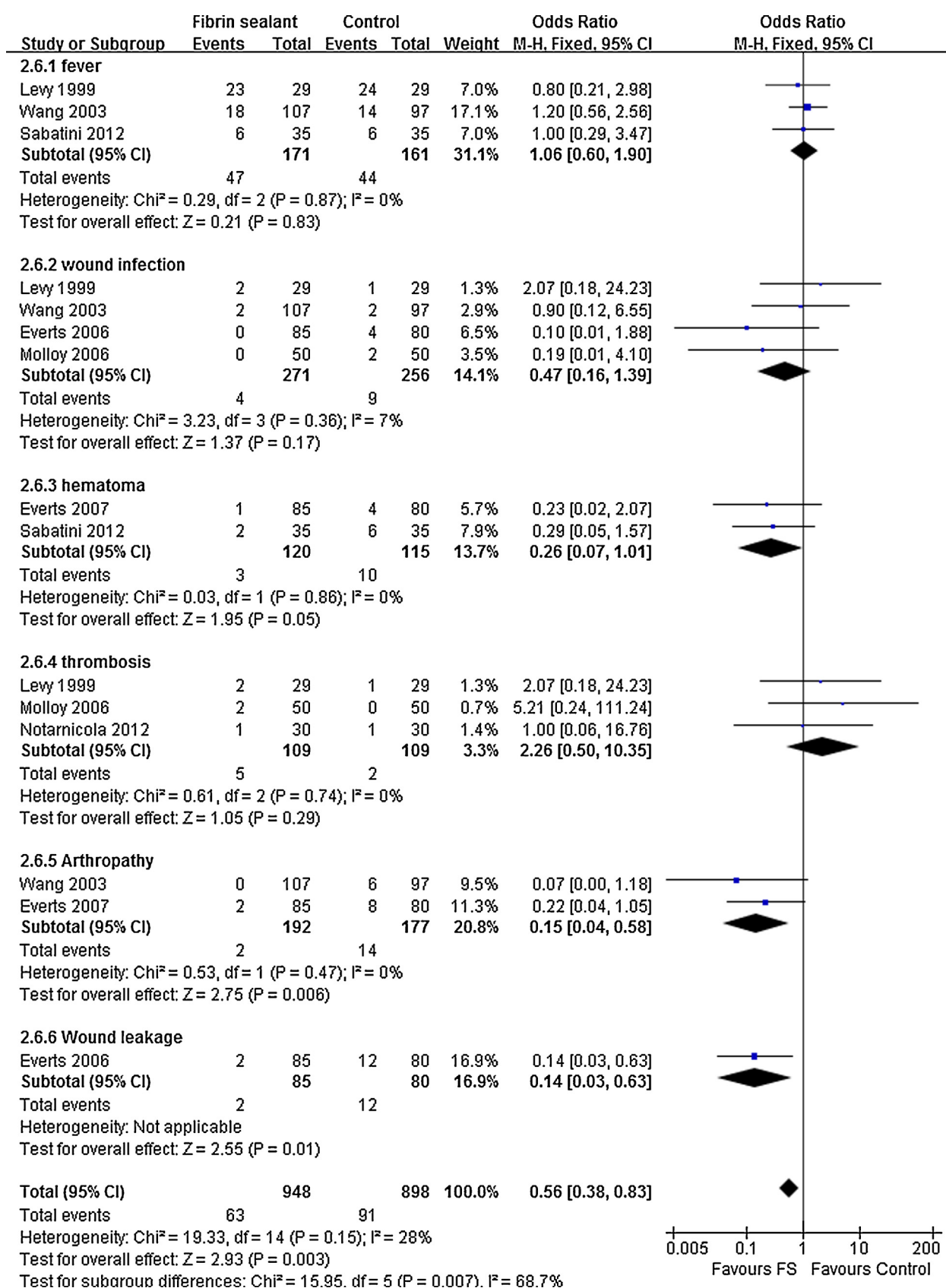


Fig. 8. Subgroup meta-analysis of the incidence of complications between the two groups.

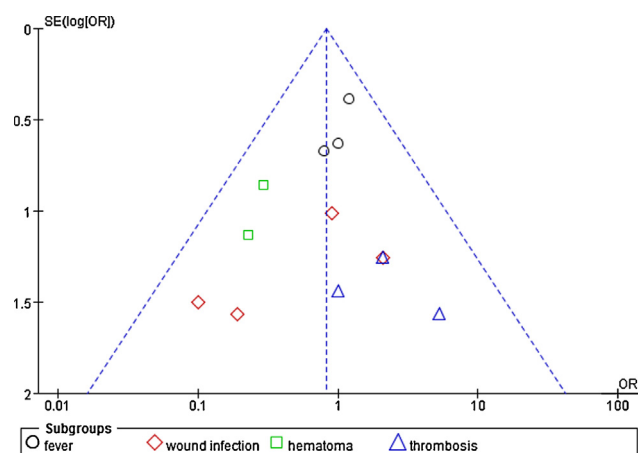


Fig. 9. Inverted funnel plot indicating publication bias of transfusion incidence.

4.2. Blood loss

Drain-out volume and/or total blood loss was adopted as outcome measures. The results demonstrated that low- and high-dose fibrin sealant significantly decreased the drain-out volume and fibrin sealant also decreased total blood loss, while it failed to reach statistical significance. Excepted for one study using Mercuriali and Inghilerri formula [19], all the other studies adopted the method of Gross [2,16,20] to calculate the total blood loss. As known, after adjusting the patients' weight and height, gross formula used the mean Hb reduction of preoperative and the lowest postoperative values, while Mercuriali and Inghilerri formula used the mean Hb reduction of preoperative and the postoperative 6 days values [24], which will get a lower total blood loss. As the calculated method was same between the treatment and control group in each study, so this may be a potential source of heterogeneity, but would not affect the pooled result.

The results showed that after using fibrin sealant, the Hb reduction and drain-out volume were both decreased. While, in the included studies, one study did not apply wound drains [13], and the drain-out volume may be affected by patient condition, the surgeons' experience, drain removal time and hidden blood loss (additional blood stasis in the soft tissue of the knee) [5,14,25–27].

Besides, four studies [2,17,22,23] reported that the range of flexion significantly improved after treatment with fibrin sealant. This subsequently contributed to a significantly shorter hospital stay, indicating that fibrin sealant can speed up knee function recovery. And one study [21], which included patients with bilateral knee osteoarthritis, reported no significant difference between the fibrin sealant group and the control group. The data could not be analyzed, because different detection times were used.

The meta-analysis indicated that fibrin sealant reduced the incidence of overall complications and a further subgroup analysis showed that the risk of hematoma, arthropathy and wound leakage was significantly reduced compared to the control group. Due to insufficient data, it was not possible to assess financial differences in our analysis, as only one study [2] performed a cost analysis. The study suggested that the cost of the additional 31 units of fibrin sealant was 9743 €, whereas the cost savings achieved by using 11 fewer blood transfusion units was only 3484 €, indicating that fibrin sealant treatment was still the more expensive option.

Subgroup analyses revealed similar results for low dosages and high dosages of fibrin sealant. The results from the low dosage subgroup should be considered carefully as there were only a small number of trials and few patients. In addition, only four RCTs [2,9,11,17] were included in the low dosage subgroup and one of these included a trial [9] that used only 2 mL of fibrin sealant; this

heterogeneity of dosage may have affected the results. Similarly, six RCTs were included in the high dosage subgroup, and one of these trials [16] used a fibrin sealant mixture that ranged from 5 mL to 10 mL and did not include a detailed description; this may also have a negative effect on the analysis. Finally, the subgroup analyses demonstrated that a high-dose of fibrin sealant resulted in effective management of postoperative bleeding, functional recovery and reduced complications. There was not enough evidence to draw a conclusion on the effectiveness of low-doses of fibrin sealant in knee surgery.

Although standard procedures for retrieval, assessment of relevance and statistical processing were performed in this meta-analysis, some potential limitations also should be taken into account:

- methodological limitations of RCTs, including and absence of blind allocation in the randomization process;
- clinical and statistical heterogeneity, including differences in patient population, the description and experience of different surgeons, outcome evaluation method and follow-up time [28];
- hospital stay in this review may not shed much light on the relative role of fibrin sealant, which was used mainly as an adjuvant bleeding prevention medicine;
- due to unpublished or unidentified clinical trials, publication bias might jeopardize the validity of this meta-analysis.

Some other possible forms of bias and potential source of heterogeneity should also be mentioned. Massin et al. [2] did not use a tourniquet intraoperative, which might increase the risk of bleeding. Levy et al. [16] did not describe detailed procedures or information about surgeons from different centres. Wang et al. [14] did not offer any information on methodology, patients' character or surgeons' experience. Skovgaard [21] included patients with serious health conditions.

In conclusion, patients undergoing knee surgery would benefit from high-dose fibrin sealant with reduced transfusion rate and unit, hospital stay and complications, while they might benefit little from it in total blood loss. However, the effects of a low-dose of fibrin in knee surgery remain inconclusive.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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